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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHAFER, SHULAMITH H	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/730,751	MANOLAGAS ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15,16 and 18-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15,16 and 18-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/1/06, 5/2/06.* 8/16/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

The amendment received 1 May 2006 in response to the Office Action of 4 April 2006 has been entered. Claims 1, 2, 4-8 and 10-18 were pending. Claims 1-12, 14 and 17 are canceled. Claims 13, 15, 16 and 18 are amended and the amendments have been entered. New claims 19-24 have been added, and entered. Upon further consideration, the requirement for election of species is withdrawn. Thus, the in vitro and in vivo methods will be rejoined and examined together. Claims 13, 15, 16, and 18-24 are under consideration. The pertinent remarks/arguments filed with the amendment received 1 May 2006 will be responded to herein.

The text of those sections of Title 35 U.S. Code not included in this action can be found in the prior Office action.

Objections/Rejections Withdrawn

The objection to claims 13-18 as encompassing non-elected invention is withdrawn in view of the rejoinder of claims to in vitro and in vivo methods.

The objection to the specification as identifying this application as a continuation of Application No. 09/413,958 is withdrawn in view of Applicants' amendment of the specification. However, application 09/413,958 is now U.S. Patent 6,660,468. Appropriate update and correction is required.

The objection to the IDS filed on 18 August 2004 is withdrawn in view of applicants' submission of copies of the references with the amendment filed 1 May 2006. These references have been duly considered. The references on the Supplemental IDS have also been considered.

The objection to the Brief Description of the Drawings is withdrawn in view of applicants' amendment to paragraph beginning at page 8, line 18.

All rejections of claims 14 and 17 are withdrawn. Applicants have cancelled these claims, thus rendering the rejections moot.

The rejection of Claims 13-18 under 35 U.S.C. 112, second paragraph is withdrawn in view of applicants' amendments to the claims.

The rejection of Claims 13-18 under 35 U.S.C. 102(b) as being anticipated by Jilka et al. (1997) is withdrawn in view of applicants' amendments to the claims and in view of applicants' arguments.

New rejections are set forth below.

New Grounds for Rejection

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 18, and 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for compounds that increase bone mineral density *in vivo,* wherein the loss of bone mineral density is a result of osteoperosis does not reasonably provide enablement for an *in vitro* method of screening for compounds that increase bone mineral density, nor a method for screening for increase in bone mineral density *in vivo* in any unspecified (non-osteoperotic) patient population or animal model.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are broadly drawn to a method of screening for compounds that increase mineral bone density. The independent claim, claim 16, recites the steps comprising:

a. contacting osteoblast and osteocyte cells with either a glucocorticoid or a test compound; and

b. comparing the number of said osteoblast and osteocyte cells undergoing apoptosis following treatment with said glucocorticoid to the number of said osteoblast and osteocyte cells undergoing apoptosis following treatment with said test compound.

wherein a lower number of apoptotic cells following treatment with said test compound than with said glucocorticoid is indicative of a compound that increases bone mineral density

Claim 22 recites wherein contacting is in vitro in cell culture; claim 23 and 24 recite wherein the contacting is in vivo, and in vivo in a murine animal model.

The specification teaches that glucocorticoid-induced bone disease, particularly glucocorticoid-induced osteoperosis in patients and in murine model, is accompanied by decreases in bone mineral density accompanied by defective osteoblastogenesis and osteoclastogenesis in bone marrow and increase in apoptosis of mature osteoblasts and osteocytes (page 3, line 15 to 18, bridging page 4, lines 1 and 2). The disclosure also teaches that treatment of mice with prednisolone resulted in decreased bone

mineral density (page 10, lines 15-18). Correlated with this decrease in bone mineral density is an increase in osteoblast and osteocyte apoptosis (page 11, lines 5-7). "Bone mineral density" refers to bone mass as defined by Dual-Energy X-Ray Absorbtiometry (DEXA) (page 12, lines 19-20).

However, the specification and working examples fail to show a nexus between a decrease in apoptotic osteoblasts and osteocytes in bone of normal patients or patients suffering from bone pathologies other than osteoperosis and increases in bone density. One of ordinary skill in the art would predict that, in normal patients, decreases in apoptosis in bone cells would lead to increases in bone formation but the newly formed bone would exhibit the same bone density as that of previously formed bone.

Additionally, the working example discloses that both osteoblast and osteoclast formation is reduced in bone marrow cultures derived from animals treated with prednisolone (Example 6, pages 18-20). The specification and working examples are silent as to the predictive relationship between decreases in apoptosis in osteoblasts and osteocytes contacted with test compound *in vitro* (compared to cells contacted with glucocorticoid) and increases in bone density. The art of record does not overcome this deficiency in the teachings of the specification. While Carbone et al. (2005, Micron 36:645-652, page 646, Figure 1) teach that long-term administration glucocorticoids result in decrease in osteoblast and preosteoblast differentiation and activity, and increase in apoptosis of osteoblasts and osteocytes, resulting in a decrease in bone formation, and bone mass, the reference is silent as to whether observations of an *in vitro* decrease in apoptosis of osteoblasts and osteocytes would correlate with an *in vivo* increase in bone density. Thus, the person of ordinary skill in the art would have to undertake undue experimentation to determine whether an *in vitro* model of reduction of apoptosis in osteoblasts and osteocytes would be predictive of increasing bone density *in vivo*.

Due to the large quantity of experimentation required to determine a nexus between decrease in apoptosis of osteoblast and osteocyte cells *in vivo* in tissue from normal individuals or individuals suffering from bone pathologies other than osteoperosis, or a decrease in apoptosis of osteoblasts and osteocytes *in vitro* and an

increase in bone mineral density, the lack of direction/guidance presented in the specification and the absence of working examples directed to correlation between changes in apoptosis in an *in vitro* model and bone mineral density, the complex nature of the invention, the state of the art that teaches a correlation between glucocorticoids, increases in apoptosis osteoblasts and osteocytes and decreases in bone mass, but is silent as to the applicability of an *in vitro* model, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention commensurate with the scope of the claims.

35 U.S.C. § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 13, 15, 16, 18, 20, 21, 23 and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Weinstein et al. (1998, J. Clin. Invest. 102:274-282, cited on IDS of 16 August 2004, page 3 of 8, AT2).

Weinstein et al. teach administering placebo (test compound) or prednisolone (glucocorticoid), a synthetic glucocorticoid analogue, to mice (page 275, column 1), thereby contacting osteoblast and osteocyte cells with a glucocorticoid or a test compound. The reference teaches that bone mineral density was lower in mice implanted with prednisolone than those found in mice implanted with placebo (test compound) (page 277, column 1, 1st paragraph) and teach counting of osteoblasts and osteocytes to determine the percentage of TUNEL-positive cells, thereby determining the percentage of cells exhibiting morphological changes typical of apoptosis (page 279, column 1, 1st and 2nd paragraphs). The reference also demonstrates apoptotic (TUNEL-positive) osteoblasts and osteocytes in patients with glucocorticoid-induced

osteoporosis (page 279, column 1, last paragraph, bridging column 2, 1st paragraph). Additionally, Weinstein teaches that synthetic glucocorticoids have been developed that exhibit anti-inflammatory activity in vivo as potently as classical glucocorticoids, and "the present demonstration of osteoblast and osteocyte apoptosis in animals and humans with glucocorticoid-induced osteoporosis predicts that these synthetic compounds will have bone sparing effects." (page 281, column 2, 4th paragraph).

Thus, Weinstein et al. anticipate all the limitations of claims 13, 15, 16, 18, 20, 23 and 24.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstein et al. as applied to claims 13, 15, 16, and 18 in view of Jilka et al. (1997, J Bone and Mineral Res. 12 (supplement) S455, abstract S411, cited in Office Action of

4 April 2006 and on IDS of 16 August 2004, page 7 of 8, AX7) and further in view of Kato et al. (1997, J Bone and Mineral Res. 12:2014-2023, cited on IDS of 16 August 2004, page 3 of 8, AX).

The teachings of Weinstein et al. are discussed in detail above. Weinstein also teaches the detection of osteoblasts in ex vivo bone marrow cultures (page 276, column 1, 2nd paragraph).

Weinstein et al. do not teach contacting osteoblast and osteocyte cells with a test compound and comparing the number of said osteoblast and osteocyte cells undergoing apoptosis following treatment with glucocorticoid to the number of said osteoblast and osteocyte cell undergoing apoptosis following treatment with test compound wherein the contacting is in vitro in cell culture.

The teachings of Jilka et al were discussed in detail in the Office Action of 4 April 2006 and are outlined below.

Jilka et al. teach incubating osteoblasts with dexamethosone (a glucocorticoid) and assessing the number of apoptotic cells. Apoptotic cells were identified by visual inspection using the TUNEL technique and quantified by a spectrophotometric assay.

Kato et al. teach the establishment of an osteocyte-like cell line, MLO-Y4 (page 2014, abstract).

It would been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made, to modify the teachings of Weinstein et al. (an *in vivo* method) utilizing an *in vitro* co-culture system including the MLO-Y4 (osteocyte) cells taught by Kato et al. with the osteoblast cells (taught by Jilka et al.), and treat the osteoblast and osteocyte cells with test compounds such as synthetic glucocorticoids suggested by Weinstein et al., comparing the effects of test compounds on osteoblast and osteocyte apoptosis, with the effects of classical glucocorticoids on osteoblast and osteocyte apoptosis. One would be motivated to do so because Weinstein et al. teach that glucocorticoids stimulate apoptosis in both osteoblast and osteocyte cells *in vivo* and predict that synthetic compounds (test compounds) will have bone sparing effects, Jilka et al. teach that dexamethasone (a glucocorticoid) promotes apoptosis of osteoblast cell, and that IL-6 (test compound) added 24 hours prior to addition of

dexamethosone prevented dexamethasone-induced apoptosis, and Kato et al. teach that the MLO-Y4 cell line would be useful for studying the means whereby ostocytes communicate with other bone cells such as osteoblasts. One would have expected success because a method of testing the effects of compounds on osteoblast cell apoptosis *in vitro* is taught by Jilka et al. and co-culturing bone cells is well known in the art (see, for exemplary purposes only, 1988, McCarthy et al. J Bone and Mineral Res. 3:401-408, abstract).

Conclusion

Due to the new grounds of rejection herein, this action is made non final. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS

LORRAINE SPECTOR
PRIMARY EXAMINER